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(54) Title: HUMANIZED ANTIBODIES THAT RECOGNIZE BETA AMYLOID PEPTIDE

(57) Abstract: The invention provides improved agents and methods for treatment of diseases associated with amyloid deposits of Aß in the brain of a patient. Preferred agents include humanized antibodies.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/46587

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K16/18 A61P25/28 A61K39/395 C12N15/13 C12N15/85
C12N5/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, SEQUENCE SEARCH, MEDLINE, BIOSIS, EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BARD F ET AL: "Peripherally administered antibodies against amyloid beta-peptide enter the central nervous system and reduce pathology in a mouse model of Alzheimer disease." NATURE MEDICINE. UNITED STATES AUG 2000, vol. 6, no. 8, August 2000 (2000-08), pages 916-919, XP002227088 ISSN: 1078-8956 abstract page 918; table 1 ---	1-68, 71-143, 146-158
X	WO 00 23082 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD., ISRAEL) 27 April 2000 (2000-04-27) figure 9 --- -/--	63,138

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2003	17/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	COVONE-VAN HEES, M

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE WPI Section Ch, Week 199534 Derwent Publications Ltd., London, GB; Class B04, AN 1995-261292 XP002227089 & JP 07 165799 A (ASAHI BREWERIES LTD), 27 June 1995 (1995-06-27) abstract	65,140
X	FRENKEL D ET AL: "HIGH AFFINITY BINDING OF MONOCLONAL ANTIBODIES TO THE SEQUENTIAL EPITOPE EFRH OF BETA-AMYLOID PEPTIDE IS ESSENTIAL FOR MODULATION OF FIBRILLAR AGGREGATION" JOURNAL OF NEUROIMMUNOLOGY, ELSEVIER SCIENCE PUBLISHERS BV, XX, vol. 95, 1999, pages 136-142, XP001001345 ISSN: 0165-5728 page 141, right-hand column, line 10-25 abstract	84-120, 122-137, 142,143, 146-154, 157,158
P,X	WO 00 72880 A (SCHENK DALE B ;YEDNOCK TED (US); BARD FREDERIQUE (US); NEURALAB LT) 7 December 2000 (2000-12-07) page 3, line 24-31 page 19, line 20-24 page 21, line 20 -page 22, line 34 examples 11,12	1-68, 71-83, 138-141, 149,155, 156
E	WO 02 088306 A (LILLY CO ELI ;TSURUSHITA NAOYA (US); VASQUEZ MAXIMILANO (US)) 7 November 2002 (2002-11-07) page 2, line 5 -page 3, line 6 page 21, line 32 -page 22, line 23 claims	1-68, 71-83, 138-141, 149,155, 156
E	WO 02 088307 A (LILLY CO ELI ;HINTON PAUL ROBERT (US); VASQUEZ MAXIMILANO (US)) 7 November 2002 (2002-11-07) page 2, line 17 -page 3, line 16 page 20, line 10-15 example 1	84-137, 142,143, 146-154, 157,158

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	KETTLEBOROUGH C A ET AL: "HUMANIZATION OF A MOUSE MONOCLONAL ANTIBODY BY CDR-GRAFTING: THE IMPORTANCE OF FRAMEWORK RESIDUES ON LOOP CONFORMATION" PROTEIN ENGINEERING, OXFORD UNIVERSITY PRESS, SURREY, GB, vol. 4, no. 7, 1 October 1991 (1991-10-01), pages 773-783, XP002048549 ISSN: 0269-2139 the whole document	1-68, 71-143, 146-158

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 01/46587

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 58-61,133-136 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 69,70,144,145
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-83,138-141,155,156 (complete) 149 (partially)

Humanized immunoglobulin (Ig) light chain and heavy chain comprising (i) variable region complementarity determining regions (CDRs) from 3D6 Ig light and heavy chain variable regions sequence set forth as seq ID. 2 and 4 respectively, and (ii) variable framework region from a human acceptor Ig light and heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 3D6 light and heavy chain variable region sequence. Furthermore, the subject matter comprises the related products and methods: chimeric Ig comprising CDRs from 3D6 Ig or antigen binding fragment thereof, comprising a variable heavy and light chain (set forth as seq. ID 8, 12 and seq. ID 5,11 respectively), humanized antibody, method of preventing or treating an amyloidogenic disease and Alzheimer in patients, pharmaceutical compositions comprising said Ig, isolated polypeptide or fragments (as referred to in claims 63-66), a variant of said polypeptide, nucleic acid, vectors and host cells to encode and produce said Ig, method to produce said Ig. Method for identifying residues amenable to substitution in a humanized 3D6 variable framework region and use of the variable sequence to produce a three dimensional image of 3D6 Ig.

2. Claims: 84-137,142-148,150-154,157,
158 (complete) 149 (partially)

Humanized immunoglobulin (Ig) light chain and heavy chain comprising (i) variable region complementarity determining regions (CDRs) from 10D5 Ig light and heavy chain variable regions sequence set forth as seq ID. 14 and 16 respectively, and (ii) variable framework region from a human acceptor Ig light and heavy chain, provided that at least one framework residue is substituted with the corresponding amino acid residue from the mouse 10D5 light and heavy chain variable region sequence. Furthermore, the subject matter comprises the related products and methods: chimeric Ig, humanized antibody, method of preventing or treating an amyloidogenic disease and Alzheimer in patients, pharmaceutical compositions comprising said Ig, isolated polypeptide, a variant of said polypeptide, nucleic acid, vectors and host cells to encode and produce said Ig, method to produce said Ig. Method for identifying residues amenable to substitution in a humanized 10D5 variable framework region and use of the variable sequence to produce a three dimensional image of 10D5 Ig.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 69,70,144,145

Present claims 69,70,144,145 relate to an extremely large number of possible products. In fact, the claims contain so many possible variants that a lack of clarity (and/or conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible. Consequently, the search has not been carried out.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internati[redacted] Application No
PCT/US 01/46587

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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